510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k112221

B. Purpose for Submission:
New assay

C. Measurand:
Anti-soluble liver antigen/liver pancreas (SLA/LP) antigen IgG antibodies

D. Type of Test:
Qualitative

E. Applicant:
EUROIMMUN US Inc.

F. Proprietary and Established Names:
EUROIMMUN Anti-SLA/LP (IgG)

G. Regulatory Information:

1. Regulation section:
   21 CFR §866.5660, Multiple autoantibodies immunological test system
2. Classification:
   Class II
3. Product code:
   NIY, autoantibodies, anti-soluble liver antigen (SLA), autoimmune hepatitis
4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended use(s):
   The EUROIMMUN Anti-SLA/LP ELISA (IgG) test kit is intended for the qualitative determination of IgG class autoantibodies against SLA/LP (soluble liver antigen/liver-pancreas antigen) in human serum and plasma. It is used as an aid in the diagnosis of autoimmune hepatitis, type 1, in conjunction with other laboratory and clinical findings.
2. Indication(s) for use:
   Same as intended use above.
3. Special conditions for use statement(s):
   For prescription use only.

4. Special instrument requirements:
   Microplate reader capable of measuring OD at 450 nm and 620 to 650 nm.

I. Device Description:

The device is packaged as a kit containing: 12 microplate strips each containing 8 antigen coated wells and frame, one cut-off calibrator (20 RU/mL), human serum-based positive and negative controls, horseradish peroxidase (HRP)-conjugated rabbit anti-human IgG, ready-to-use sample buffer, 10x wash buffer concentrate, 3,3',5,5' tetramethylbenzidine (TMB) substrate and sulfuric acid stop solution.

J. Substantial Equivalence Information:

1. Predicate device name(s) and k number(s):
   INOVA Quanta Lite SLA ELISA, k021482
2. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	Detection of anti-SLA/LP IgG autoantibodies to "aid in the diagnosis of autoimmune hepatitis, type 2".	Same
Assay	ELISA	Same
Antigen	Recombinant SLA/LP	Same
Substrate	TMB	Same
Controls	One Positive Control One Negative Control	Same

Differences		
Item	**Device**	**Predicate**
Assay Type	Qualitative	Semi-quantitative
Conjugate	Rabbit anti-human IgG labeled with HRP	Goat anti-human IgG labeled with HRP
Calibrators and Controls	1 cut-off calibrator 2 controls: 1 positive, 1 negative	3 controls: 1 high positive, 1 low positive, 1 negative
Sample Matrix	Serum or plasma (EDTA, heparin, and citrate)	Serum only
Reported Units	Ratio	U/mL
Cut-Off Level	Ratio 1.0	25 U/mL

K. Standard/Guidance Document Referenced (if applicable):

CEN 13640:2002, Stability Testing of *In Vitro* Diagnostic Reagents.

L. Test Principle:

The test wells are coated with recombinant SLA/LP. The cut-off calibrator, controls, and diluted patient samples are added to the wells and autoantibodies recognizing the antigen bind during the first incubation. After washing the wells to remove all unbound proteins, conjugate is added. The conjugate binds to the captured human autoantibodies. Excess unbound conjugate is removed by another wash step. The bound conjugate is visualized with TMB substrate. Microtiter plates are read at 450 nm and a reference wavelength of 620 to 650 nm. The controls and patient results are interpreted by comparing them as a ratio of the cut-off.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The reproducibility of the assay was assessed using patient sera with a range of values. Intra-assay reproducibility was assessed by 20 determinations on one day while inter-assay reproducibility was based on 24 determinations performed over six different days. The same samples were used in both experiments. The expected result was determined from the sample mean. The results that correctly matched the expected result were tallied. The results are summarized in the tables below:

Intra-assay reproducibility:

Sample #	Sample Mean Ratio	Ratio Range	Expected Result	# Correct Results
1	0.2	0.2 – 0.2	Neg	20/20
2	0.4	0.4 – 0.4	Neg	20/20
3	0.9	0.8 – 0.9	Neg	20/20
4	1.1	1.1 – 1.2	Pos	20/20
5	1.3	1.1 – 1.4	Pos	20/20
6	1.6	1.5 – 1.7	Pos	20/20
7	3.6	3.4 – 3.7	Pos	20/20
8	4.9	4.6 – 5.3	Pos	20/20

Inter-assay reproducibility:

Sample #	Sample Mean Ratio	Ratio Range	Expected Result	# Correct Results
1	0.2	0.2 – 0.3	Neg	24/24
2	0.4	0.3 – 0.4	Neg	24/24
3	0.8	0.8 – 0.9	Neg	24/24
4	1.2	1.0 – 1.3	Pos	24/24
5	1.2	1.0 – 1.3	Pos	24/24
6	1.7	1.6 – 1.8	Pos	24/24
7	3.9	3.4 – 4.2	Pos	24/24
8	5.4	4.7 – 5.8	Pos	24/24

Lot-to-lot reproducibility was assessed using patient sera with a range of values. Each sample/lot combination was tested between six and 38 times. The expected result was determined from the sample mean. The results that correctly matched the expected result were tallied. The results are summarized in the table below:

Sample	Sample Mean Ratio	Ratio Range	Lots Tested	Runs /Lot	Total Replicates	Expected Result	# Correct Results
1	5.6	5.4 – 6.0	3	2	6	Pos	6/6
2	7.6	7.3 – 8.0	3	2	6	Pos	6/6
3	9.7	9.5 – 9.9	3	2	6	Pos	6/6
4	0.9	0.9 – 0.9	3	2	6	Neg	6/6
5	3.1	2.1 – 4.1	38	1	38	Pos	38/38
6	3.9	3.2 – 4.6	38	1	38	Pos	38/38
7	0.1	0.1 – 0.2	16	1	16	Neg	16/16
8	0.1	0.1 – 0.2	10	1	10	Neg	10/10
9	0.1	0.1 – 0.2	10	1	10	Neg	10/10

b. *Linearity/assay reportable range:*
Not applicable.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
There are no international standards for SLA/LP antibodies. Sample results are expressed as ratios of the cut-off calibrator.

Calibrators and Controls:
The cut-off calibrator and controls are derived from human serum and match pre-specified performance criteria. Each lot of cut-off calibrator and controls are traceable to a master lot.

Stability studies:
Stability studies are conducted in accordance to CEN 13640:2002. Three production lots of all kit reagents were tested. Real-time stability studies (+2°C to +8°C) support a 12-month unopened stability claim. Other studies support that the re-constituted wash buffer is stable for up to 28 days, and the opened reagents stored at +2°C to +8°C are stable for 12 months.

Sample stability:
The sponsor recommends following the guidelines in CLSI H18-A3 for sample storage.

d. *Detection limit:*
Not applicable.

e. *Analytical specificity:*

Endogenous interferents:
Five samples containing various levels of anti-SLA/LP levels were spiked

with varying concentrations of hemoglobin up to 1,000 mg/dL, triglycerides up to 2,000 mg/dL, or bilirubin up to 40 mg/dL. Comparison of all spiked sample/interferent combinations to the unspiked sample was within ±15% of the original sample concentration except one; a sample with a ratio of 1.0 spiked with 40 mg/dL bilirubin had 119% recovery. Lower concentrations of bilirubin in the same sample showed recovery ±10% of the unspiked sample.

Cross-reactivity with anti-LKM-1:
Twenty-eight (28) sera serologically positive for anti-LKM-1 antibodies were tested with the assay and found negative for anti-SLA/LP antibodies suggesting that antibodies specific for anti-LKM-1 do not bind to the SLA/LP antigen coating the assay wells. Sample ratios ranged from 0.1 to 0.7.

f. Assay cut-off:
The assay cut-off is 1.0. Results ≥ 1.0 are positive.

2. Comparison studies:

a. Method comparison with predicate device:
One hundred and sixty-seven (167) clinically characterized samples were tested with the predicate device and the EUROIMMUN Anti-SLA/LP ELISA (IgG). These samples were from patients with autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), AIH/PBC overlap syndrome, and viral hepatitis. Twenty-three (23) samples intended to challenge the assay cut-off were created by mixing positive and negative samples.

		Predicate			
		Positive	Borderline	Negative	Total
EUROIMMUNE Anti-SLA/LP ELISA	Positive	30	1	5	36
	Negative	0	0	154	58
	Total	30	1	159	190

If borderline sample is considered positive:

Positive agreement	31/31 = 100%	95% CI: 89.0% – 100%
Negative agreement	154/159 = 96.9%	95% CI: 92.8% – 98.6%

If borderline sample is considered negative:

Positive agreement	30/30 = 100%	95% CI: 88.6% – 100%
Negative agreement	154/160 = 96.2%	95% CI: 92.1% – 98.3%

b. Matrix comparison:
The purpose of this study was to demonstrate that the new devices give the same results for lithium heparin plasma, citrate plasma and EDTA plasma as for serum samples collected from the same patient. Normal sample pairs were spiked with anti-SLA/LP positive sera to create 16 samples that spanned the assay range. Serum sample ratios ranged from 0.3 – 8.9. As compared to serum samples, bias of the heparin plasma, citrate plasma and EDTA plasma

samples ranged from 89% to 113%, 90% to 120%, and 88% to 115%, respectively.

3. Clinical studies:

   a. Clinical Sensitivity and Specificity:
   Five hundred and fifteen (515) clinically characterized samples from several university, hospital, and private laboratories were analyzed with the EUROIMMUN Anti-SLA/LP ELISA (IgG) test to assess the clinical sensitivity and specificity. The patient samples consisted of 65 AIH-1, 68 AIH-2, 111 PBC, 15 AIH/PBC overlap syndrome, 47 hepatitis B, 71 hepatitis C, 19 primary sclerosing cholangitis (PSC), 24 steatohepatitis, 14 toxic liver damage, and 81 samples from other autoimmune diseases.

		Autoimmune Hepatitis Type 1		
		Positive	Negative	Total
Anti-SLA/LP	Positive	18	3*	21
	Negative	47	447	494
	Total	65	450	515

* Samples were from AIH/PBC patients

Sensitivity: 27.7% (18/65) 95% CI: 18.3% – 39.6 %
Specificity: 99.3% (447/450) 95% CI: 98.1% – 100.0%

The results for non-AIH-1 subjects are shown below:

Results by Diagnosis	Anti-SLA/LP (IgG)	
	n	Positive (%)
Autoimmune hepatitis type 2 (AIH-2)	68	0 (0.0%)
AIH/PBC overlap syndrome	15	3 (20.0%)
Viral hepatitis	118	0 (0.0%)
Toxic liver damages	14	0 (0.0%)
Steatohepatitis	24	0 (0.0%)
Primary biliary liver cirrhosis (PBC)	111	0 (0.0%)
Primary sclerosing cholangitis (PSC)	19	0 (0.0%)
Other autoimmune diseases*	81	0 (0.0%)

* Other autoimmune diseases include: MCTD, celiac disease, Type 1 diabetes, Hashimoto thyroiditis, Graves' disease, and ulcerative colitis

   b. Other clinical supportive data:
   Not applicable.

4. Clinical cut-off**:**
   Not applicable.

5. Expected values/Reference range:
   The levels of anti-SLA/LP antibodies in 150 apparently healthy blood donor samples (Caucasian, mixed age and sex) were analyzed with the EUROIMMUN Anti-SLA/LP ELISA (IgG). No samples were positive, and ratios ranged from 0 to 0.8.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.